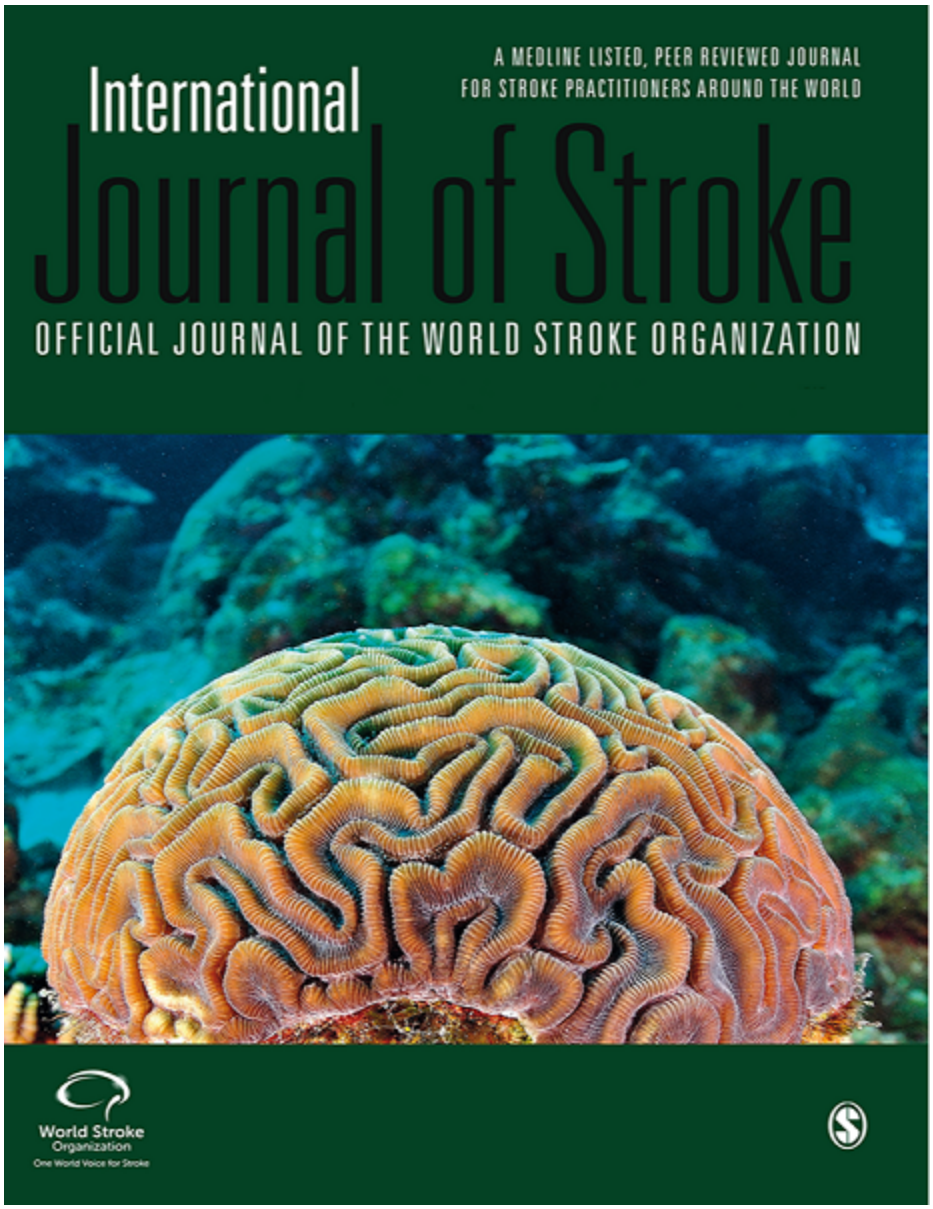

Fluoxetine for reducing disability after stroke: meta-analysis of randomised controlled trials

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Complete List of Authors:	Mead, Gillian; University of Edinburgh, Geriatric Medicine

	Legg, Lynn; University of Strathclyde, Tilney, Russel; Mater Dei Hospital, Department of Medicine Hsieh, Cheng Fang; Kaohsiung Medical University Hospital, Division of Geriatrics and Gerontology, Department of Internal Medicine and Department of Neurology Wu, Simiao; University of Edinburgh, Centre for Clinical Brain Sciences; Sichuan University, West China Hospital, Department of Neurology Lundström, Erik; Karolinska Institutet, Department of Clinical Neuroscience, Department of Neurology Rudberg, Ann-Sofie; Karolinska Institutet, Department of Clinical Neurosciences Kutlubaev, Mansur; Bashkir State Medical University Dennis, Martin; Western General Hospital, 8Dept. of Clinical Neurosciences; Soleimani, Babak; NHS Lothian Barugh, Amanda; NHS Lothian Hackett, Maree; The George Institute for Global Health, Neurological & Mental Health Division, The University of Sydney; The University of Central Lancashire, School of Health Hankey, Graeme; University of Western Australia Faculty of Medicine Dentistry and Health Sciences

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Authors: Gillian E Mead, MD, FRCP; Lynn Legg, PhD; Russel Tilney, MD; Cheng Fang Hsieh, MD; Simiao Wu, MD, PhD; Erik Lundström, MD, PhD; Ann-Sofie Rudberg MD; Mansur Kutlubaev MD, PhD; Martin S Dennis MD; Babak Soleimani MB ChB; Amanda Barugh PhD; Maree L. Hackett PhD; Graeme J Hankey MD, FRACP

Gillian E Mead, Geriatric Medicine, University of Edinburgh

Lynn Legg, Department of Medicine for the Elderly, Royal Alexandra Hospital, Paisley

Russel Tilney, Department of Medicine, Mater Dei Hospital, Malta

Cheng Fang Hsieh, Division of Geriatrics and Gerontology, Department of Internal Medicine and Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

Simiao Wu, Department of Neurology, West China Hospital, Sichuan University, Chengdu, China 610041

Erik Lundström, Karolinska Institutet, Department of Clinical Neuroscience, and adjunct senior lecturer at Department of Neuroscience, Neurology, Uppsala University, Sweden

Ann Sofie Rudberg, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Mansur Kutlubaev, Department of Neurology, G.G. Kuvatov Republican Clinical Hospital; Department of Neurology, Bashkir State Medical University, Ufa, Russia

Martin S Dennis, Centre for Clinical Brain Sciences, University of Edinburgh

Babak Soleimani, NHS Lothian

Amanda Barugh, NHS Lothian

Maree L. Hackett, Faculty of Medicine, UNSW Sydney; The George Institute for Global Health, Australia; The University of Central Lancashire

Graeme J Hankey, Medical School, The University of Western Australia

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Corresponding Author:
Gillian E Mead
Geriatric Medicine
University of Edinburgh
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh EH16 4SA
Gillian.E.Mead@ed.ac.uk

Tables and Figures

Objective: To determine whether fluoxetine, at any dose, given within the first year after stroke to patients who did not have to have mood disorders at randomisation led to a reduction in disability, dependency, neurological deficits and fatigue; improved motor function, mood, and cognition at the end of treatment and follow-up, with the same number or fewer adverse effects.

Methods: Searches in July 2018 included several databases, trials registers, reference lists, contact with experts. We excluded RCTs requiring patients to have mood disorder at randomisation. Co-primary outcomes were dependence and disability. Dichotomous data were synthesised using risk ratios (RR) and continuous data using standardised mean differences (SMD). Quality was appraised using Cochrane risk of bias methods. Sensitivity analyses explored influence of study quality.

Results: The searches identified 3412 references of which 491 full texts were assessed for eligibility. Six new completed RCTs (n=3710) were eligible, making a total of 13 trials (n=4145). There was no difference in the proportion independent at the end of treatment (3 trials, n=3249, 36·6% fluoxetine vs 36·7% control; RR 1·00, 95% confidence interval 0·91 to 1.09, p=0·99, I^2 78%) and no difference in disability (7 trials n=3404, SMD 0·05, -0·02 to 0·12 p=0·15, I^2=81%). Fluoxetine was associated with better neurological scores and less depression but more seizures. Among the four (n=3283) high quality RCTs, the only difference between groups was lower depression scores with fluoxetine.

Conclusion: Fluoxetine does not reduce disability and dependency after stroke. It improves depression scores but increases seizures. Ongoing RCTs will determine its effects in stroke vary depending on ethnicity, background treatment and other factors.

Classification of evidence: meta-analysis

Background and purpose

Worldwide, stroke is the second leading cause of death, the third leading cause of disability [1], and results in 6.5 million years being lived with disability [2]. Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) which has been used for many years to treat mood disorders, including post-stroke depression. A 2010 systematic review suggested that fluoxetine might improve recovery in stroke patients without depression [3]. In 2011, a randomised controlled trial (RCT) recruiting 118 patients with hemiparesis due to recent (5-10 days previously) ischaemic stroke reported better motor recovery and reduced dependency with 3 months treatment with fluoxetine [4], possibly by promotion of neurogenesis [5], neuroprotection [6], modulation of cerebral motor activity [7] and prevention of depression. A 2012 Cochrane systematic review of SSRIs for stroke recovery suggested that fluoxetine reduced disability after stroke even in patients without depression, but poor methodological trial quality probably introduced bias [8]. Since then one large (n=3127) trial of fluoxetine for stroke recovery has been published [9]. Meta-analyses should be updated as soon as there are new studies that might change the conclusions of the review.

Objective

We sought to determine whether fluoxetine, at any dose, given within the first year after stroke to patients who did not have to have mood disorders at randomisation, reduced disability, dependency, neurological deficits and fatigue, and improved motor function, mood, and cognition at the end of treatment and follow-up, with the same number or fewer adverse effects.

Methods

Protocol and registration

We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). Data supporting this review are available from the corresponding author.

We did not register the current review on PROSPERO as we used the same methods as the 2012 Cochrane review, except for a) including only fluoxetine trials b) excluding trials requiring patients to have mood disorders at randomisation, c) simplifying our sensitivity analyses by excluding trials at high or unclear risk of bias in at least one domain rather than considering each domain individually, d) excluding trials comparing fluoxetine plus another 'active treatment' versus the 'active treatment' and e) defining incomplete outcome data reporting as systematic differences in withdrawals between groups rather than a total of >5%. These five criteria (a-e) were agreed prior to study selection and data extraction.

After study selection and data extraction, but prior to analyses, we decided to report the proportion independent (modified Rankin score, mRS 0-2) rather than the proportion dependent (mRS 3-5).

Random effects models were used in the 2012 Cochrane review because we assumed that the included studies would represent a random sample of the effect sizes that could be observed. As the large Fluoxetine or Control Under Supervision (FOCUS) trial had systematically different results from the smaller trials, a random effects model would have given disproportionate weight to smaller studies [10]. Therefore we report fixed effects models. We performed sensitivity analyses using random effects models and report any major differences between the two.

Eligibility criteria

Participants: stroke in the previous year. Stroke was defined as sudden-onset focal neurological disturbance, assumed to be vascular in origin, and lasting more than 24 hours [11]. We excluded trials requiring patients to have a mood disorder at randomisation.

Types of intervention: any dose of fluoxetine, any mode of delivery, given for any duration.

Comparator arm was usual care or a placebo. We excluded studies comparing fluoxetine plus another 'active treatment' versus 'active treatment' alone, because of possible interactions.

Outcomes We pre-specified two co-primary outcomes: independence or disability at the end of treatment (using any measure). Improvements in disability (performance of activities of daily living) could be important to patients even without a change in overall dependence.

Secondary outcomes: independence and disability at the end of follow-up. Neurological score, depression, anxiety, cognition, quality of life, fatigue, healthcare costs, death, motor scores, adverse events (at the end of treatment and/or at the end of follow-up), 'leaving the trial before scheduled follow-up' which included any reason other than death for missing outcome data.

Report characteristics: We included all reports irrespective of year of publication, language and publication status. Where necessary we sought unpublished data from authors.

Information sources

Searches were performed:

Cochrane Stroke Group Trials Register (17 July 2018);

* Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2018, Issue 6);

* MEDLINE Ovid (from 1948 to 17 July 2018);

* Embase Ovid (from 1980 to 17 July 2018);

* CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; from 1982 to 17 July 2018);

* AMED (Allied and Complementary Medicine; from 1985 to 17 July 2018);

* PsycINFO Ovid (from 1967 to 17 July 2018).

* US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov); and * World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch) on 26th June 2018.

We screened reference lists from review articles and included papers. We contacted experts to identify additional studies.

Study selection

Duplicate references were removed using COVIDENCE software (www.covidence.org). Titles and abstracts were scrutinised by two authors. Obviously irrelevant articles were excluded.

Full texts of potentially relevant articles were retrieved and inclusion criteria applied by two authors. A third author was involved if there was disagreement. We included studies meeting our criteria.

Data collection process

Two reviewers independently extracted data from the new trials using COVIDENCE. We contacted the authors if data were missing or required in a different format.

Data items

Continuous and dichotomous data were extracted. If trials reported the same number of patients at beginning and end, we assumed there had been no deaths. If there was no

description of how adverse events were recorded, we included any available data on adverse events, but did not assume the absence of serious adverse events unless the authors had explicitly reported this. If there was a different number of patients at the end of the trial, we extracted data on deaths and drop-outs for other reasons. The denominator was the number of patients for whom a particular outcome was available.

Risk of bias of individual studies

Two authors using the same criteria as previously [8]. We included allocation (selection bias), blinding (performance bias and detection bias), incomplete outcome data (systematic differences between groups in withdrawals from a study), selective reporting and other potential sources of bias.

Pre-specified sensitivity analyses

Sensitivity analyses explored the influence of bias by excluding studies with unclear or high risk of bias across one or more key domains [10].

Summary measures and synthesis of results

Risk ratios (RRs) were used for dichotomous data and for ordinal scales with an established cut-point. Standardised mean differences (SMD) were used for continuous data and ordinal scales with no standard cut-point. We pre-specified our interpretation of SMD: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect [10].

One trial [12] reported medians, interquartile ranges and ranges. We estimated the mean and standard deviation (SD) using the best available method [13].

Risk of bias across studies

Funnel plot was used to investigate publication bias. When available, we scrutinised protocols to investigate selective reporting.

Subgroup analyses

Because fluoxetine may be more effective when given earlier after stroke, we aimed to explore the influence of time since stroke at recruitment on our primary outcome by categorising studies as less than three months, three to six months, six to nine months, nine to 12 months.

Results

From the database searches, we identified 3412 references, removed 426 duplicates, screened 2988 references, and assessed 500 full texts for eligibility (figure 1). Three published papers had the same grant number [14-16], very similar inclusion criteria and recruited patients from the same hospital during overlapping time periods; one appeared to be the three year follow-up data [16] from one of the earlier publications [15]. Thus we included the publication with the largest number of patients reporting our pre-specified outcomes [15] and categorised the other two [14,16] as 'awaiting assessment' pending further information. We identified three further new eligible trials from the database searches [12, 17, 18] and one by contact with experts [19]. We also included FOCUS [9].

These six new trials (n=3710) [9, 12, 15, 17-19] were added to seven eligible trials [4, 20-25] (n=435) identified in the 2012 Cochrane review (total 13 completed trials, n=4145, table 1). One further registered trial was withdrawn because it recruited no patients [27].

Several ongoing RCTs together aim to recruit about 3775 patients (appendix).

Risk of Bias

There were four high quality trials (n=3283) with a low risk of bias across important quality criteria [4, 9,12,18] (figure 2). One terminated early having recruited 6 patients, and reported no deaths [18]. The Funnel plot for disability showed no clear evidence of publication bias (available on request).

Results of studies and synthesis of results

Co-primary outcomes: independence and disability at end of treatment (figures 3 and 4).

Three trials (n=3249) reported independence. Fixed effects meta-analysis found no difference in the proportion independent (36.6% in fluoxetine vs 36.7% control; RR 1.00, 95% confidence interval 0.91 to 1.09, p=0.99, I^2 78%) and no difference in disability (7 trials n=3404, SMD 0.05 (-0.02 to 0.12) p=0.15, I^2=81%).

Two other trials [19, 26] reported improvements in mRS in the fluoxetine group but the data were in a format that could not be used in the meta-analysis and the authors did not respond to our requests for clarification.

Random effects models demonstrated a small, but statistically significant benefit of fluoxetine on disability (SMD 0.34, 0.04 to 0.64, p=0.03, I^2=81%); and a higher RR (RR 1.87 (0.74 to 4.56; p=0.19, I^2=78%) of being independent than the fixed effects models because of the greater weight given to smaller positive trials.

Secondary outcomes at end of treatment: summary effect sizes (table 2)

Fluoxetine was associated with better neurological scores (8 trials, n=803, SMD -0.28 (-0.42 to -0.14) p=<0.001, I^2 77%), better depression scores (6 trials n=3113 SMD -0.16 (-0.23 to -0.09) p<0.0001, I^2 92%), fewer diagnoses of depression (2 trials n=3194 RR 0.77 (0.65 to 0.90) p=0.001, I^2=53%) but more seizures (7 trials n=3815, 3.9% vs 2.6% RR 1.49 (1.05 to 2.11) p=0.03, I^2=0). Random effects models gave broadly similar results. FOCUS identified a slight excess of bone fractures in the fluoxetine group which was statistically significant. No other trial reported fractures.

End of follow-up

Two trials (n=2924) reported disability at end of follow up: SMD was 0.11 (-0.17 to 0.40) p=0.45, I^2=85% (fixed effects).

Sensitivity analyses: high quality trials only (table 3), fixed effects

Fixed effects models found a small, but statistically significant effect on depression scores at end of treatment (2 trials, n=2861, -0.11 (-0.19 to -0.04) p=0.002, I^2=69%). Random effects found a slightly larger effect size for depression which was not statistically significant (-0.23 (-0.56 to 0.10) p=0.07, I^2 61%).

Subgroup analyses

We did not perform subgroup analyses because all trials except two (n=68) recruited patients within three months of stroke onset.

Discussion

This systematic review of fluoxetine for stroke recovery identified 14 trials recruiting more than 4000 patients of which four (n=3283) were of high methodological quality.

There were no differences between groups for the co-primary outcomes of dependency and disability. Fluoxetine was associated with better neurological scores at the end of treatment, better depression scores and fewer diagnoses of depression, although the effect sizes were all small and there was substantial heterogeneity. There was a higher risk of seizures with fluoxetine. However, when only high quality trials were considered, the only statistically significant difference between groups was better (lower) depression scores at the end of treatment.

We used fixed effect models as these give appropriate weight to larger trials. The sensitivity analysis using random effects models found a spuriously large benefit of fluoxetine on independence (RR 1.87) because of the disproportionate weight given to smaller trials. Fixed and random effect models produced only slightly different effect sizes for depression scores.

Previous meta-analyses suggested that fluoxetine might reduce dependency and disability if given early after stroke [3, 8, 28]. This current meta-analysis, which included many more patients than previous reviews, has not confirmed these promising effects. Although one of the reviews [28] strongly recommended fluoxetine to promote neurological recovery, this recommendation was based on the results of just four reports [4, 14, 15, 22], only one of which was high quality [4].

Thus, these data do not support the routine prescription of fluoxetine early after stroke in order to reduce dependency and disability [29,30]. Clinicians and patients may wish to

consider the routine use of fluoxetine early after stroke for its small effects on depression, but this would need to be weighed up against the excess of seizures and bone fractures.

There are some limitations at study and outcome level: only four trials were of high methodological quality, not all had been registered prospectively or reported the same outcomes. Furthermore, different scales were used for the same outcome; although we used SMD to combine data, the interpretation of SMD is not intuitive, and clinicians prefer to know the effect size on a familiar scale (e.g. Functional Independence Measure). Two large ongoing trials (AFFINITY and EFFECTS) [31] are using the same measures as FOCUS. A future meta-analysis will report mean difference for continuous data.

We did not register the review in PROSPERO, but we used almost the same methods as the 2012 Cochrane review. We used sensitive searches developed by Cochrane Stroke, there was complete retrieval of identified research, no language restrictions and inclusion of unpublished data [12].

About three-quarters of the patients were from the FOCUS trial performed in the National Health Service, UK). There was quite marked heterogeneity, even for the high quality trials (table 3); this might be explained by the different types of patients and healthcare settings. Five of the low quality trials were from China [15, 17, 21, 22, 23]; the three reporting disability all found favourable effects of fluoxetine. As the evidence base increases, it may be possible to perform meta-regression analyses to determine the factors (such as country, health care setting and trial quality) associated with good outcome.

Ongoing trials will provide information about the external validity of these results in other stroke populations with respect to ethnicity, background treatment and healthcare systems. AFFINITY [31] is recruiting patients from Vietnam and includes Asian populations. Also, further information is needed on other outcomes (e.g. depression, anxiety, cognition, bone

fractures, fatigue, health care costs and other potential adverse effects) that are of importance to patients, clinicians and policy makers, and to determine whether any benefits or harms at the end of treatment persist to the end of follow-up.

When AFFINITY and EFFECTS are published, we will update the meta-analysis of fluoxetine for stroke recovery, and will also perform an individual patient meta-analysis.

Our searches identified several completed trials of other SSRIs in stroke patients with and without depression and other mood disorders, which will be included in the next update of the Cochrane review of SSRIs for stroke recovery.

Finally, it would be a significant waste of resources if further trials of fluoxetine in stroke are started before ongoing trials have reported and been included in a future meta-analysis [32].

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Table 1 Characteristics of the randomised controlled trials (RCTs) that are included in this review

Study	Country	Participants (pathological type and time since stroke)	Number recruited	Number included at end of treatment	Dose and duration of fluoxetine	Control	Outcomes reported by the trial authors	Follow-up period
Birchenall 2018	France	Stroke or brain haemorrhage, day 3 to day 15	6 (study terminated early)	6	20mg daily for 3 months	Placebo	Several clinical and TMS measurements, death.	End of treatment and at month 6
Chollet 2011	France	Ischaemic stroke, 5-10 days	118	113	20mg daily for 3 months	Matching placebo	Primary outcome: FMMS. Secondary endpoints: NIHSS, mRS and MADRS at 0, 30 and 90 days. AEs	End of treatment
Dam 1996	Italy	Ischaemic stroke, 1-6 months	35	33	20mg daily for 12 weeks	Matching placebo	HDRS, HSS (total, gait and motor scores), BI, death, AEs	End of treatment
FOCUS collaborators 2018	UK	Any stroke, 2-15 days	3127	3106	20mg daily for 6 months	Matching placebo	Primary: mRS. Secondary: SIS, depression, MHI5, fatigue, Euroquol 5D 5L, health care costs	End of treatment and then 6 months later
He 2004	China	First ever stroke, all pathological types. Mean time 3.1 days in fluoxetine and 3.5days in control	84	71	20mg daily for 8 weeks	Usual stroke care	HAMD, SSS. AEs	End of treatment
He 2016	China	Ischaemic stroke, within 1 week	374	350	20mg for 90 days	Usual care	NIHSS, BI; AEs	End of treatment,

								and at day 180
Kong 2006	China	Any pathological type, within 7 days	90	73	20mg for 8 weeks	Matching placebo	HAMD, BI, NIHSS. Somatic side effects and hyponatraemia	End of treatment
Li 2004	China	Any pathological type, mean time to recruitment was 2 days	67	67	20mg daily for 4 weeks	Routine stroke care	HAMD, CSS; AEs in fluoxetine group	End of treatment
Marquez-Romero 2013	Mexico	Intracerebral haemorrhage within 10 days	32	30	20mg daily for 90 days	Matching placebo	Primary: FMMS, mRS Secondary: NIHSS, BI, AEs	End of treatment
Pariente 2001	France	Lacunar ischaemic stroke	8	8	Single 20mg dose	Placebo	Finger tapping and clinical scales presented only as graphs. fMRI activation location	Post-treatment
Robinson 2000 (follow up reported in Mikami 2011)	USA and Argentina	All pathological types, within 6 months	33	28	Dose increased over 3 weeks from 10mg to 30mg daily; total 12 weeks	Matching placebo	HDRS, mRS, FIM, MMSE, JHFI, death, AEs	End of treatment
Shah 2016	India	Haemorrhagic stroke, 5-10 days after onset	89	84	10mg for one week, increased to 20mg after one week,	Inert capsule ‘similar’ to fluoxetine	Primary outcome: FMMS mRS and AEs	End of treatment

Zhao 2011	China	Stroke with aphasia, 'early treatment with fluoxetine', precise time not stated	82	71	total 3 months 20mg for 12 weeks	Standard care	MESS, ADL	End of treatment

ADL: Activities of Daily Living
AE: Adverse Events
BI: Barthel Index
CSS: Chinese Stroke Scale
FIM: Functional Independence Measure
FMMS: Fugl-Meyer Motor Scale
fMRI: functional magnetic resonance imaging
HAMD/HDRS: Hamilton Depression Rating Scale
HSS: Hemispheric Stroke Scale
JHFI: Johns Hopkins Functioning Inventory
MADRS: Montgomery-Åsberg Depression Rating Scale
MMSE: Mini Mental State Examination
MESSS: Modified Edinburgh-Scandinavian Stroke Scale
mRS: modified Rankin Score
MHI5 Mental Health Inventory 5
NIHSS: National Institutes of Health Stroke Scale
SSS: Scandinavian Stroke Scale
SIS: Stroke Impact Scale
TMS: Transmagnetic stimulation

Table 2 Effects sizes from meta-analysis of primary and secondary outcomes; end of treatment; from all trials using fixed effects models, where at least two trials provided data that could be included.

	Number of trials (number of participants) contributing to the meta-analysis	**Effect size (RR or SMD) and 95% CI**	**P value**	**I^2**
Independent (modified Rankin score 0-2)	3 trials (n=3249)	RR1.00 (0.91 to 1.09)	0.99	78%
Disability	7 trials (n=3404)	SMD 0.05 (-0.02 to 0.12)	0.15	81%
Neurological deficit score	8 trials (n=803)	SMD -0.28 (-0.42 to -0.14)	<0.0001	77%
Depression-continuous data	6 trials (n=3113)	SMD -0.16 (-0.23 to -0.09)	<0.0001	92%
Depression-dichotomous	2 trials (n=3194)	RR 0.77 (0.65 to 0.90)	0.001	53%
Motor score	5 trials (n=3079)	SMD 0.06 (-0.02 to 0.13)	0.12	95%
Cognition	2 trials (n=2834)	SMD -0.04 (-0.11 to 0.03)	0.32	0%
Death	11 trials (n=3824)	RR 1.0 (0.79 to1.26)	1.00	0%
Cognition	2 trials (n=2793)	SMD -0.04 (-0.11 to 0.03)	0.3	0%
Seizures	7 trials (n=3815)	RR 1.49 (1.05 to 2.11)	0.03	0%
Gastrointestinal symptoms (nausea, diarrhoea, abdominal pain)	7 trials (n=688)	RR 1.38 (0.99 to 1.94)	0.06	8%
Serious bleeding	2 trials (n=3477)	RR 1.10 (0.72 to 1.62)	0.67	0%
Leaving before the end of first follow-up	11 trials (n=3972)	RR 0.92 (0.61 to 1.40)	0.71	0%

RR: relative risk

SMD: standardised mean difference

Table 3

Summary effect sizes for trials at low risk of bias, at end of treatment, where at least two trials reported the outcome of interest. Fixed effects models

	Number of trials and participants contributing to the meta-analysis	**Effect size**	**P value**	**I^2**
Independent (modified Rankin score 0-2)	3 trials (n=3269)	RR1.00 (0.91 to 1.09)	0.99	78%
Disability	2 trials (n=2853)	SMD -0.01 (-0.09 to 0.06)	0.75	0%
Neurological deficit score	2 trials (n=142)	SMD -0.30 (-0.63 to 0.04)	0.08	0%
Depression (continuous data)	2 trials (n=2861)	SMD -0.11 (-0.19 to -0.04)	0.002	69%
Motor score	3 trials (n=2936)	SMD 0.02 (-0.05 to 0.09)	0.58	88%
Death	4 trials (n=3260)	RR 0.99 (0.79 to 1.25)	0.95	0%
Gastrointestinal symptoms	2 trials (n=148)	RR 2.19 (1.0 to 4.76)	0.05	0%
Leaving the trial before first follow-up	4 trials (n=3283)	RR 1.01 (0.48 to 2.10)	0.98	0%
Seizures	3 trials (n=3275)	RR 1.47 (0.99 to 2.18)	0.06	0%

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Professor Peter Sandercock commented on the manuscript

Contributions of authors

Gillian Mead conceived the study, screened references, extracted data, assessed risk of bias, performed the analyses and wrote the first draft.

Lynn Legg searched for studies selected studies for inclusion, collected data, assessed risk of bias, managed studies through the review process, contributed to the final version.

Russel Tilney, Cheng Fang Hsieh, Simiao Wu, Erik Lundström, Ann-Sofie Rudberg, Mansur Kutlubaev, Babak Soleimani and Amanda Barugh screened citations, retrieved potentially relevant papers and screened their eligibility for the systematic review, assisted with data extraction and drafted the manuscript for submission

Maree Hackett extracted data, and edited the final manuscript.

Graeme J. Hankey and Martin Dennis, conceived the study, provided expertise in relation to analysis methods, and edited the draft paper.

Figure 1

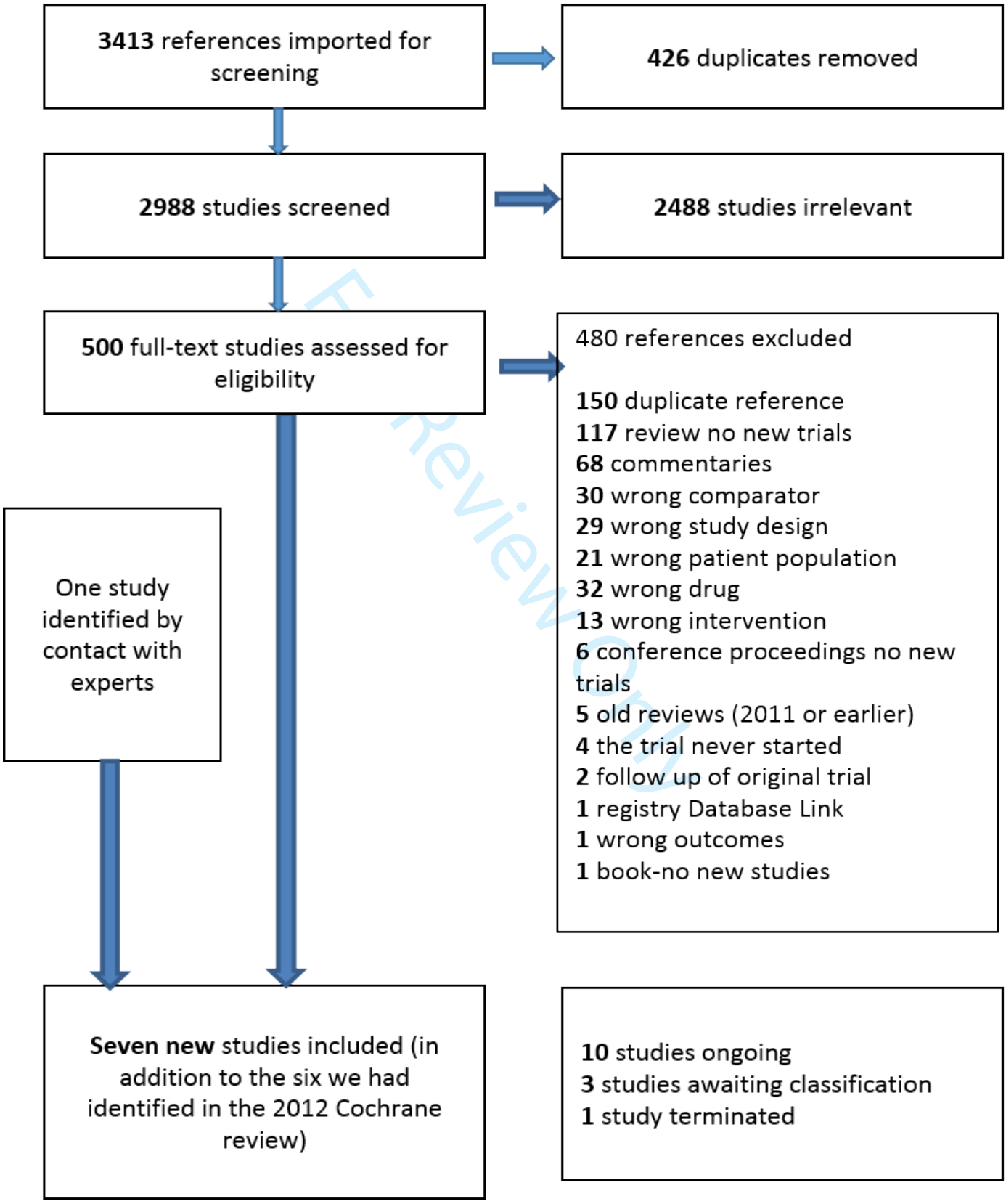


Figure 2

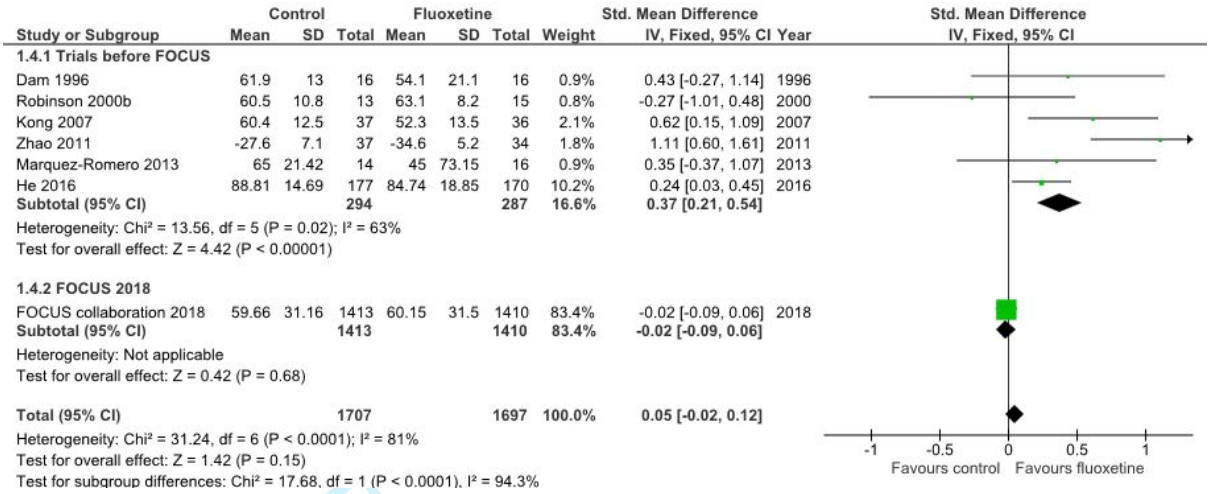


Figure 3

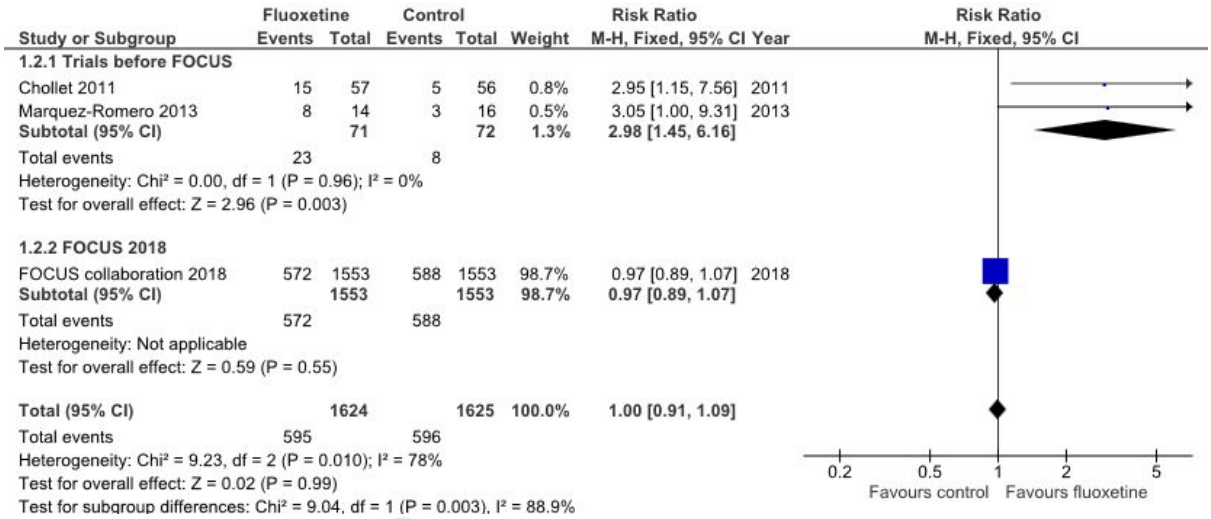
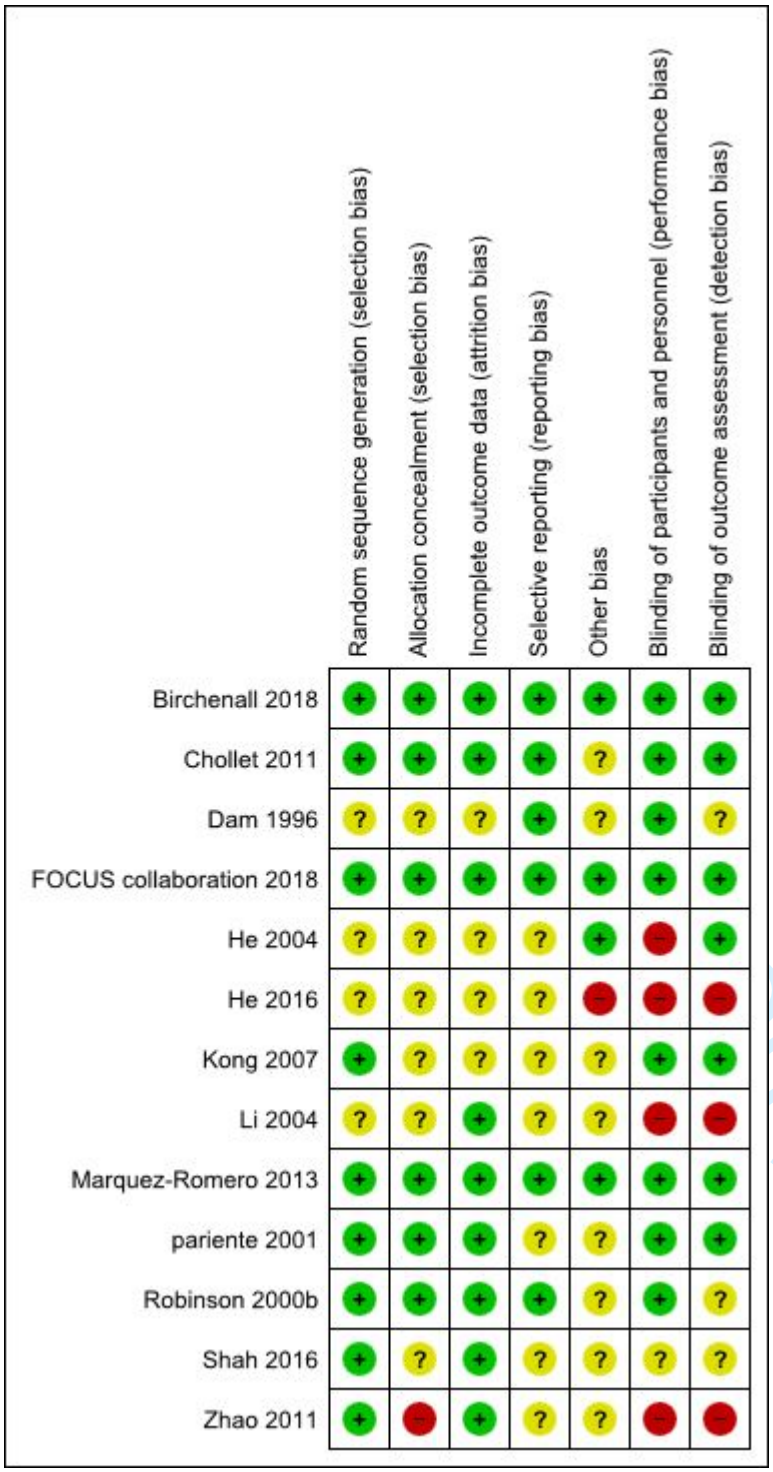


Figure 4


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Birchenall 2018
Chollet 2011
Dam 1996
FOCUS collaboration 2018
He 2004
He 2016
Kong 2007
Li 2004
Marquez-Romero 2013
pariente 2001
Robinson 2000b
Shah 2016
Zhao 2011

Fluoxetine for stroke recovery: meta-analysis of randomised controlled trials

Gillian E Mead, MD, FRCP. Professor of Stroke and Elderly Care Medicine, University of Edinburgh

Lynn Legg, PhD. Senior researcher, Department of Medicine for the Elderly, Royal Alexandra Hospital, Paisley

Russel Tilney, MD, Department of Neuroscience, Mater Dei Hospital, Malta

Cheng Fang Hsieh, MD, Division of Geriatrics and Gerontology, Department of Internal Medicine and Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

Simiao Wu, MD, PhD, Department of Neurology, West China Hospital, Sichuan University, Chengdu, China 610041

Erik Lundström, Associate Professor of Neurology; Karolinska Institutet, Department of Clinical Neuroscience, and adjunct senior lecturer at Department of Neuroscience, Neurology, Uppsala University, Sweden

Ann Sofie Rudberg MD, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Mansur Kutlubaev MD, PhD, Department of Neurology, G.G. Kuvatov Republican Clinical Hospital; Department of Neurology, Bashkir State Medical University, Ufa, Russia

Martin S Dennis Professor of Stroke Medicine. University of Edinburgh

Babak Soleimani MB ChB Clinical Fellow, NHS Lothian

Amanda Barugh PhD. Consultant Stroke Physician. NHS Lothian

Maree L. Hackett PhD. Program Head Mental Health. Professor, Faculty of Medicine, UNSW Sydney. Professor of Epidemiology, The University of Central Lancashire, United Kingdom. The George Institute for Global Health, UNSW, Australia

Graeme J. Hankey MD, FRACP Professor of Neurology, Medical School, The University of Western Australia

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Corresponding author

Gillian E Mead, Centre for Clinical Brain Sciences, University of Edinburgh, Royal Infirmary, Little France Crescent, Edinburgh EH16 4SA gillian.e.mead@ed.ac.uk

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Table 2 Effects sizes from meta-analysis of primary and secondary outcomes; end of treatment; from all trials using fixed effects models, where at least two trials provided data that could be included

Table 3 Summary effect sizes for trials at low risk of bias, at end of treatment, where at least two trials reported the outcome of interest. Fixed effects models

Figure 1. Flow diagram showing selection of studies

Figure 2 Risk of Bias

Figure 3. Forest plot, mRS (0-2) at end of treatment

Figure 4. Forest plot, disability at end of treatment

Objective: To determine whether fluoxetine, at any dose, given within the first year after stroke to patients who did not have to have mood disorders at randomisation reduced disability, dependency, neurological deficits and fatigue; improved motor function, mood, and cognition at the end of treatment and follow-up, with the same number or fewer adverse effects.

Methods: Searches (from 2012) in July 2018 included databases, trials registers, reference lists, contact with experts. Co-primary outcomes were dependence and disability. Dichotomous data were synthesised using risk ratios (RR) and continuous data using standardised mean differences (SMD). Quality was appraised using Cochrane risk of bias methods. Sensitivity analyses explored influence of study quality.

Results: The searches identified 3412 references of which 491 full texts were assessed for eligibility. Six new completed RCTs (n=3710) were eligible, and were added to the seven trials identified in a 2012 Cochrane review (total: 13 trials, n=4145). There was no difference in the proportion independent (3 trials, n=3249, 36.6% fluoxetine vs 36.7% control; RR 1.00, 95% confidence interval 0.91 to 1.09, p=0.99, I^2 78%) nor in disability (7 trials n=3404, SMD 0.05, -0.02 to 0.12 p=0.15, I^2=81%) at end of treatment. Fluoxetine was associated with better neurological scores and less depression. Among the four (n=3283) high quality RCTs, the only difference between groups was lower depression scores with fluoxetine.

Conclusion: This class I evidence demonstrates that fluoxetine does not reduce disability and dependency after stroke but improves depression.

Background and purpose (word count 240)

Worldwide, stroke is the second leading cause of death, the third leading cause of disability [1], and results in 6.5 million years being lived with disability [2]. Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) which has been used for many years to treat mood disorders, including post-stroke depression. A 2010 systematic review suggested that fluoxetine might improve recovery in stroke patients without depression [3]. In 2011, a randomised controlled trial (RCT) recruiting 118 patients with hemiparesis due to recent (5-10 days previously) ischaemic stroke reported better motor recovery and reduced dependency with 3 months treatment with fluoxetine [4], possibly by promotion of neurogenesis [5], neuroprotection [6], modulation of cerebral motor activity [7] and prevention of depression. A 2012 Cochrane systematic review of SSRIs for stroke recovery suggested that fluoxetine reduced disability after stroke even in patients without depression, but poor methodological trial quality probably introduced bias [8]. **In December 2018, one very** large (n=3127) trial of fluoxetine for stroke recovery was published [9]. Meta-analyses should be updated as soon as there are new studies that might change the conclusions of the review. **In this paper, we report the meta-analysis of fluoxetine for stroke recovery. The Cochrane review of SSRI for stroke recovery will be updated subsequently.**

Objective

We sought to determine whether fluoxetine, at any dose, given within the first year after stroke to patients who did not have to have mood disorders at randomisation, reduced disability, dependency, neurological deficits and fatigue, and improved motor function, mood, and cognition at the end of treatment and follow-up, with the same number or fewer adverse effects.

Methods

Protocol and registration

We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). Data supporting this review are available from the corresponding author.

We did not register this review on PROSPERO as we used the same methods as the 2012 Cochrane review, except for a) including only fluoxetine trials b) excluding trials requiring patients to have mood disorders at randomisation, c) simplifying our sensitivity analyses by excluding trials at high or unclear risk of bias in at least one domain rather than considering each domain individually, d) excluding trials comparing fluoxetine plus another 'active treatment' versus the 'active treatment' and e) defining incomplete outcome data reporting as systematic differences in withdrawals between groups rather than a total of >5%. These five criteria (a-e) were agreed prior to study selection and data extraction. After study selection and data extraction, but prior to analyses, we decided to report the proportion independent (modified Rankin score, mRS 0-2) rather than the proportion dependent (mRS 3-5).

Random effects models had been used in the 2012 Cochrane review because we assumed that the included studies would represent a random sample of the effect sizes that could be observed. As the large Fluoxetine or Control Under Supervision (FOCUS) trial had systematically different results from the smaller trials, a random effects model would have given disproportionate weight to smaller studies [10]. Therefore we report fixed effects models. We performed sensitivity analyses using random effects models and report any major differences between the two.

Eligibility criteria

Participants: stroke in the previous year. Stroke was defined as sudden-onset focal neurological disturbance, assumed to be vascular in origin, and lasting more than 24 hours [11]. We excluded trials requiring patients to have a mood disorder at randomisation.

Types of intervention: any dose of fluoxetine, any mode of delivery, given for any duration.

Comparator arm was usual care or a placebo. We excluded studies comparing fluoxetine plus another 'active treatment' versus 'active treatment' alone, because of possible interactions.

Outcomes We pre-specified two co-primary outcomes: independence or disability at the end of treatment (using any measure). Improvements in disability (performance of activities of daily living) could be important to patients even without a change in overall dependence.

Secondary outcomes: independence and disability at the end of follow-up. Neurological score, depression, anxiety, cognition, quality of life, fatigue, healthcare costs, death, motor scores, adverse events (at the end of treatment and/or at the end of follow-up), 'leaving the trial before scheduled follow-up' which included any reason other than death for missing outcome data.

Report characteristics: We included all reports irrespective of year of publication, language and publication status. Where necessary we sought unpublished data from authors.

Information sources

Searches were performed:

Cochrane Stroke Group Trials Register (17 July 2018);

* Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2018, Issue 6);

* MEDLINE Ovid (from 1948 to 17 July 2018);

* Embase Ovid (from 1980 to 17 July 2018);

* CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; from 1982 to 17 July 2018);

* AMED (Allied and Complementary Medicine; from 1985 to 17 July 2018);

* PsycINFO Ovid (from 1967 to 17 July 2018).

* US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov); and * World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch) on 26th June 2018.

We screened reference lists from review articles and included papers. We contacted experts to identify additional studies.

Study selection

Duplicate references were removed using COVIDENCE software (www.covidence.org). Titles and abstracts were scrutinised by two authors. Obviously irrelevant articles were excluded.

Full texts of potentially relevant articles were retrieved and inclusion criteria applied by two authors. A third author was involved if there was disagreement. We included studies meeting our criteria.

Data collection process

Two reviewers independently extracted data from the new trials using COVIDENCE. We contacted the authors if data were missing or required in a different format.

Data items

Continuous and dichotomous data were extracted. If trials reported the same number of patients at beginning and end, we assumed there had been no deaths. If there was no

description of how adverse events were recorded, we included any available data on adverse events, but did not assume the absence of serious adverse events unless the authors had explicitly reported this. If there was a different number of patients at the end of the trial, we extracted data on deaths and drop-outs for other reasons. The denominator was the number of patients for whom a particular outcome was available.

Risk of bias of individual studies

Two authors using the same criteria as previously [8]. We included allocation (selection bias), blinding (performance bias and detection bias), incomplete outcome data (systematic differences between groups in withdrawals from a study), selective reporting and other potential sources of bias.

Pre-specified sensitivity analyses

Sensitivity analyses explored the influence of bias by excluding studies with unclear or high risk of bias across one or more key domains [10].

Summary measures and synthesis of results

Risk ratios (RRs) were used for dichotomous data and for ordinal scales with an established cut-point. Standardised mean differences (SMD) were used for continuous data and ordinal scales with no standard cut-point. We pre-specified our interpretation of SMD: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect [10].

One trial [12] reported medians, interquartile ranges and ranges. We estimated the mean and standard deviation (SD) using the best available method [13].

Risk of bias across studies

Funnel plot was used to investigate publication bias. When available, we scrutinised protocols to investigate selective reporting.

Subgroup analyses

Because fluoxetine may be more effective when given earlier after stroke, we aimed to explore the influence of time since stroke at recruitment on our primary outcome by categorising studies as less than three months, three to six months, six to nine months, nine to 12 months.

Results

From the database searches, we identified 3412 references, removed 426 duplicates, screened 2988 references, and assessed 500 full texts for eligibility (figure 1). Three published papers had the same grant number [14-16], very similar inclusion criteria and recruited patients from the same hospital during overlapping time periods; one appeared to be the three year follow-up data [16] from one of the earlier publications [15]. Thus we included the publication with the largest number of patients reporting our pre-specified outcomes [15] and categorised the other two [14,16] as 'awaiting assessment' pending further information. We identified three further new eligible trials from the database searches [12, 17, 18] and one by contact with experts [19]. We also included FOCUS [9].

These six new trials (n=3710) [9, 12, 15, 17-19] were added to seven eligible trials [4, 20-25] (n=435) identified in the 2012 Cochrane review (total 13 completed trials, n=4145, table 1). One further registered trial was withdrawn because it recruited no patients [27].

Several ongoing RCTs together aim to recruit about 3775 patients (appendix).

Risk of Bias

There were four high quality trials (n=3283) with a low risk of bias across important quality criteria [4, 9,12,18] (figure 2). One terminated early having recruited 6 patients, and reported no deaths [18]. The Funnel plot for disability showed no clear evidence of publication bias (available on request).

Results of studies and synthesis of results

Co-primary outcomes: independence and disability at end of treatment (figures 3 and 4).

Three trials (n=3249) reported independence. Fixed effects meta-analysis found no difference in the proportion independent (36.6% in fluoxetine vs 36.7% control; RR 1.00, 95% confidence interval 0.91 to 1.09, p=0.99, I^2 78%) and no difference in disability (7 trials n=3404, SMD 0.05 (-0.02 to 0.12) p=0.15, I^2=81%).

Two other trials [19, 26] reported improvements in mRS in the fluoxetine group but the data were in a format that could not be used in the meta-analysis and the authors did not respond to our requests for clarification.

Random effects models demonstrated a small, but statistically significant benefit of fluoxetine on disability (SMD 0.34, 0.04 to 0.64, p=0.03, I^2=81%); and a higher RR (RR 1.87 (0.74 to 4.56; p=0.19, I^2=78%) of being independent than the fixed effects models because of the greater weight given to smaller positive trials.

Secondary outcomes at end of treatment: summary effect sizes (table 2)

Fluoxetine was associated with better neurological scores (8 trials, n=803, SMD -0.28 (-0.42 to -0.14) p=<0.001, I^2 77%), better depression scores (6 trials n=3113 SMD -0.16 (-0.23 to -0.09) p<0.0001, I^2 92%), fewer diagnoses of depression (2 trials n=3194 RR 0.77 (0.65 to 0.90) p=0.001, I^2=53%) but more seizures (7 trials n=3815, 3.9% vs 2.6% RR 1.49 (1.05 to 2.11) p=0.03, I^2=0). Random effects models gave broadly similar results. FOCUS identified a slight excess of bone fractures in the fluoxetine group which was statistically significant. No other trial reported fractures.

End of follow-up

Two trials (n=2924) reported disability at end of follow up: SMD was 0.11 (-0.17 to 0.40) p=0.45, I^2=85% (fixed effects).

Sensitivity analyses: high quality trials only (table 3), fixed effects

Fixed effects models found a small, but statistically significant effect on depression scores at end of treatment (2 trials, n=2861, -0.11 (-0.19 to -0.04) p=0.002, I^2=69%). Random effects found a slightly larger effect size for depression which was not statistically significant (-0.23 (-0.56 to 0.10) p=0.07, I^2 61%).

Subgroup analyses

We did not perform subgroup analyses because all trials except two (n=68) recruited patients within three months of stroke onset.

Discussion

This systematic review of fluoxetine for stroke recovery identified 14 trials recruiting more than 4000 patients of which four (n=3283) were of high methodological quality.

There were no differences between groups for the co-primary outcomes of dependency and disability. Fluoxetine was associated with better neurological scores at the end of treatment, better depression scores and fewer diagnoses of depression, although the effect sizes were all small and there was substantial heterogeneity. There was a higher risk of seizures with fluoxetine. However, when only high quality trials were considered, the only statistically significant difference between groups was better (lower) depression scores at the end of treatment.

We used fixed effect models as these give appropriate weight to larger trials. The sensitivity analysis using random effects models found a spuriously large benefit of fluoxetine on independence (RR 1.87) because of the disproportionate weight given to smaller trials. Fixed and random effect models produced only slightly different effect sizes for depression scores.

Previous meta-analyses suggested that fluoxetine might reduce dependency and disability if given early after stroke [3, 8, 28]. This current meta-analysis, which included many more patients than previous reviews, has not confirmed these promising effects. Although one of the reviews [28] strongly recommended fluoxetine to promote neurological recovery, this recommendation was based on the results of just four reports [4, 14, 15, 22], only one of which was high quality [4].

Thus, these data do not support the **routine p**rescription of fluoxetine early after stroke in order to reduce dependency and disability [29,30]. Clinicians and patients may wish to consider the routine use of fluoxetine early after stroke for its small effects on depression, but

this would need to be weighed up against the excess of seizures and bone fractures. **This review has not addressed the question about whether fluoxetine is of benefit to stroke survivors with mood disorders-this will be addressed by other systematic reviews and meta-analyses which are currently being updated.**

There are some limitations at study and outcome level: only four trials were of high methodological quality, not all had been registered prospectively or reported the same outcomes. Furthermore, different scales were used for the same outcome; although we used SMD to combine data, the interpretation of SMD is not intuitive, and clinicians prefer to know the effect size on a familiar scale (e.g. Functional Independence Measure). Two large ongoing trials (AFFINITY and EFFECTS) [31] are using the same measures as FOCUS. A future meta-analysis will report mean difference for continuous data.

We did not register the review in PROSPERO, but we used almost the same methods as the 2012 Cochrane review. We used sensitive searches developed by Cochrane Stroke, there was complete retrieval of identified research, no language restrictions and inclusion of unpublished data [12].

About three-quarters of the patients were from the FOCUS trial performed in the National Health Service, UK). **In FOCUS, entry criteria were broad and patients did not have to have motor deficits, as in the FLAME trial. However, the subgroup analysis of patients with motor deficits recruited to FOCUS found no evidence of an effect on either the mRS or motor score of the Stroke Impact Scale.**

There was quite marked heterogeneity, even for the high quality trials (table 3); this might be explained by the different types of patients and healthcare settings. Five of the low quality trials were from China [15, 17, 21, 22, 23]; the three reporting disability all found favourable effects of fluoxetine. As the evidence base increases, it may be possible to perform meta-

regression analyses to determine the factors (such as country, health care setting and trial quality) associated with good outcome. **We did not pre-specify other outcomes that might plausibly be influenced by fluoxetine such as sleep quality and irritability, though we noted that the included trials did not measure these outcomes.**

Ongoing trials with a very similar protocol to FOCUS, which have recruited patients from different parts of the world, will provide information about the external validity of these results in other stroke populations with respect to ethnicity, background treatment and healthcare systems. AFFINITY [31] recruited patients from Vietnam and includes Asian populations and EFFECTS recruited from Sweden. Also, further information is needed on other outcomes (e.g. depression, anxiety, cognition, bone fractures, fatigue, health care costs and other potential adverse effects) that are of importance to patients, clinicians and policy makers, and to determine whether any benefits or harms at the end of treatment persist to the end of follow-up.

When AFFINITY and EFFECTS are published, we will update the meta-analysis of fluoxetine for stroke recovery, and will also perform an individual patient meta-analysis.

Our searches identified several completed trials of other SSRIs in stroke patients with and without depression and other mood disorders, which will be included in the next update of the Cochrane review of SSRIs for stroke recovery.

Finally, before any further trials of fluoxetine for stroke recovery are started/funded, it would be prudent to wait for the results of AFFINITY and EFFECTS [32].

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Table 1 Characteristics of the randomised controlled trials (RCTs) that are included in this review

Study	Country	Participants (pathological type and time since stroke)	Number recruited	Number included at end of treatment	Dose and duration of fluoxetine	Control	Outcomes reported by the trial authors	Follow-up period
Birchenall 2018	France	Stroke or brain haemorrhage, day 3 to day 15	6 (study terminated early)	6	20mg daily for 3 months	Placebo	Several clinical and TMS measurements, death.	End of treatment and at month 6
Chollet 2011	France	Ischaemic stroke, 5-10 days	118	113	20mg daily for 3 months	Matching placebo	Primary outcome: FMMS. Secondary endpoints: NIHSS, mRS and MADRS at 0, 30 and 90 days. AEs	End of treatment
Dam 1996	Italy	Ischaemic stroke, 1-6 months	35	33	20mg daily for 12 weeks	Matching placebo	HDRS, HSS (total, gait and motor scores), BI, death, AEs	End of treatment
FOCUS collaborators 2018	UK	Any stroke, 2-15 days	3127	3106	20mg daily for 6 months	Matching placebo	Primary: mRS. Secondary: SIS, depression, MHI5, fatigue, Euroquol 5D 5L, health care costs	End of treatment and then 6 months later
He 2004	China	First ever stroke, all pathological types. Mean time 3.1 days in fluoxetine and 3.5days in control	84	71	20mg daily for 8 weeks	Usual stroke care	HAMD, SSS. AEs	End of treatment
He 2016	China	Ischaemic stroke, within 1 week	374	350	20mg for 90 days	Usual care	NIHSS, BI; AEs	End of treatment,

								and at day 180
Kong 2006	China	Any pathological type, within 7 days	90	73	20mg for 8 weeks	Matching placebo	HAMD, BI, NIHSS. Somatic side effects and hyponatraemia	End of treatment
Li 2004	China	Any pathological type, mean time to recruitment was 2 days	67	67	20mg daily for 4 weeks	Routine stroke care	HAMD, CSS; AEs in fluoxetine group	End of treatment
Marquez-Romero 2013	Mexico	Intracerebral haemorrhage within 10 days	32	30	20mg daily for 90 days	Matching placebo	Primary: FMMS, mRS Secondary: NIHSS, BI, AEs	End of treatment
Pariente 2001	France	Lacunar ischaemic stroke	8	8	Single 20mg dose	Placebo	Finger tapping and clinical scales presented only as graphs. fMRI activation location	Post-treatment
Robinson 2000 (follow up reported in Mikami 2011)	USA and Argentina	All pathological types, within 6 months	33	28	Dose increased over 3 weeks from 10mg to 30mg daily; total 12 weeks	Matching placebo	HDRS, mRS, FIM, MMSE, JHFI, death, AEs	End of treatment
Shah 2016	India	Haemorrhagic stroke, 5-10 days after onset	89	84	10mg for one week, increased to 20mg after one week,	Inert capsule ‘similar’ to fluoxetine	Primary outcome: FMMS mRS and AEs	End of treatment

Zhao 2011	China	Stroke with aphasia, 'early treatment with fluoxetine', precise time not stated	82	71	total 3 months 20mg for 12 weeks	Standard care	MESS, ADL	End of treatment

ADL: Activities of Daily Living
AE: Adverse Events
BI: Barthel Index
CSS: Chinese Stroke Scale
FIM: Functional Independence Measure
FMMS: Fugl-Meyer Motor Scale
fMRI: functional magnetic resonance imaging
HAMD/HDRS: Hamilton Depression Rating Scale
HSS: Hemispheric Stroke Scale
JHFI: Johns Hopkins Functioning Inventory
MADRS: Montgomery-Åsberg Depression Rating Scale
MMSE: Mini Mental State Examination
MESSS: Modified Edinburgh-Scandinavian Stroke Scale
mRS: modified Rankin Score
MHI5 Mental Health Inventory 5
NIHSS: National Institutes of Health Stroke Scale
SSS: Scandinavian Stroke Scale
SIS: Stroke Impact Scale
TMS: Transmagnetic stimulation

Table 2 Effects sizes from meta-analysis of primary and secondary outcomes; end of treatment; from all trials using fixed effects models, where at least two trials provided data that could be included.

	Number of trials (number of participants) contributing to the meta-analysis	**Effect size (RR or SMD) and 95% CI**	**P value**	**I^2**
Independent (modified Rankin score 0-2)	3 trials (n=3249)	RR1.00 (0.91 to 1.09)	0.99	78%
Disability	7 trials (n=3404)	SMD 0.05 (-0.02 to 0.12)	0.15	81%
Neurological deficit score	8 trials (n=803)	SMD -0.28 (-0.42 to -0.14)	<0.0001	77%
Depression-continuous data	6 trials (n=3113)	SMD -0.16 (-0.23 to -0.09)	<0.0001	92%
Depression-dichotomous	2 trials (n=3194)	RR 0.77 (0.65 to 0.90)	0.001	53%
Motor score	5 trials (n=3079)	SMD 0.06 (-0.02 to 0.13)	0.12	95%
Cognition	2 trials (n=2834)	SMD -0.04 (-0.11 to 0.03)	0.32	0%
Death	11 trials (n=3824)	RR 1.0 (0.79 to1.26)	1.00	0%
Cognition	2 trials (n=2793)	SMD -0.04 (-0.11 to 0.03)	0.3	0%
Seizures	7 trials (n=3815)	RR 1.49 (1.05 to 2.11)	0.03	0%
Gastrointestinal symptoms (nausea, diarrhoea, abdominal pain)	7 trials (n=688)	RR 1.38 (0.99 to 1.94)	0.06	8%
Serious bleeding	2 trials (n=3477)	RR 1.10 (0.72 to 1.62)	0.67	0%
Leaving before the end of first follow-up	11 trials (n=3972)	RR 0.92 (0.61 to 1.40)	0.71	0%

RR: relative risk

SMD: standardised mean difference

Table 3

Summary effect sizes for trials at low risk of bias, at end of treatment, where at least two trials reported the outcome of interest. Fixed effects models

	Number of trials and participants contributing to the meta-analysis	**Effect size**	**P value**	**I^2**
Independent (modified Rankin score 0-2)	3 trials (n=3269)	RR1.00 (0.91 to 1.09)	0.99	78%
Disability	2 trials (n=2853)	SMD -0.01 (-0.09 to 0.06)	0.75	0%
Neurological deficit score	2 trials (n=142)	SMD -0.30 (-0.63 to 0.04)	0.08	0%
Depression (continuous data)	2 trials (n=2861)	SMD -0.11 (-0.19 to -0.04)	0.002	69%
Motor score	3 trials (n=2936)	SMD 0.02 (-0.05 to 0.09)	0.58	88%
Death	4 trials (n=3260)	RR 0.99 (0.79 to 1.25)	0.95	0%
Gastrointestinal symptoms	2 trials (n=148)	RR 2.19 (1.0 to 4.76)	0.05	0%
Leaving the trial before first follow-up	4 trials (n=3283)	RR 1.01 (0.48 to 2.10)	0.98	0%
Seizures	3 trials (n=3275)	RR 1.47 (0.99 to 2.18)	0.06	0%

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Professor Peter Sandercock commented on the manuscript

Contributions of authors

Gillian Mead conceived the study, screened references, extracted data, assessed risk of bias, performed the analyses and wrote the first draft.

Lynn Legg searched for studies selected studies for inclusion, collected data, assessed risk of bias, managed studies through the review process, contributed to the final version.

Russel Tilney, Cheng Fang Hsieh, Simiao Wu, Erik Lundström, Ann-Sofie Rudberg, Mansur Kutlubaev, Babak Soleimani and Amanda Barugh screened citations, retrieved potentially relevant papers and screened their eligibility for the systematic review, assisted with data extraction and drafted the manuscript for submission

Maree Hackett extracted data, and edited the final manuscript.

Graeme J. Hankey and Martin Dennis, conceived the study, provided expertise in relation to analysis methods, and edited the draft paper.

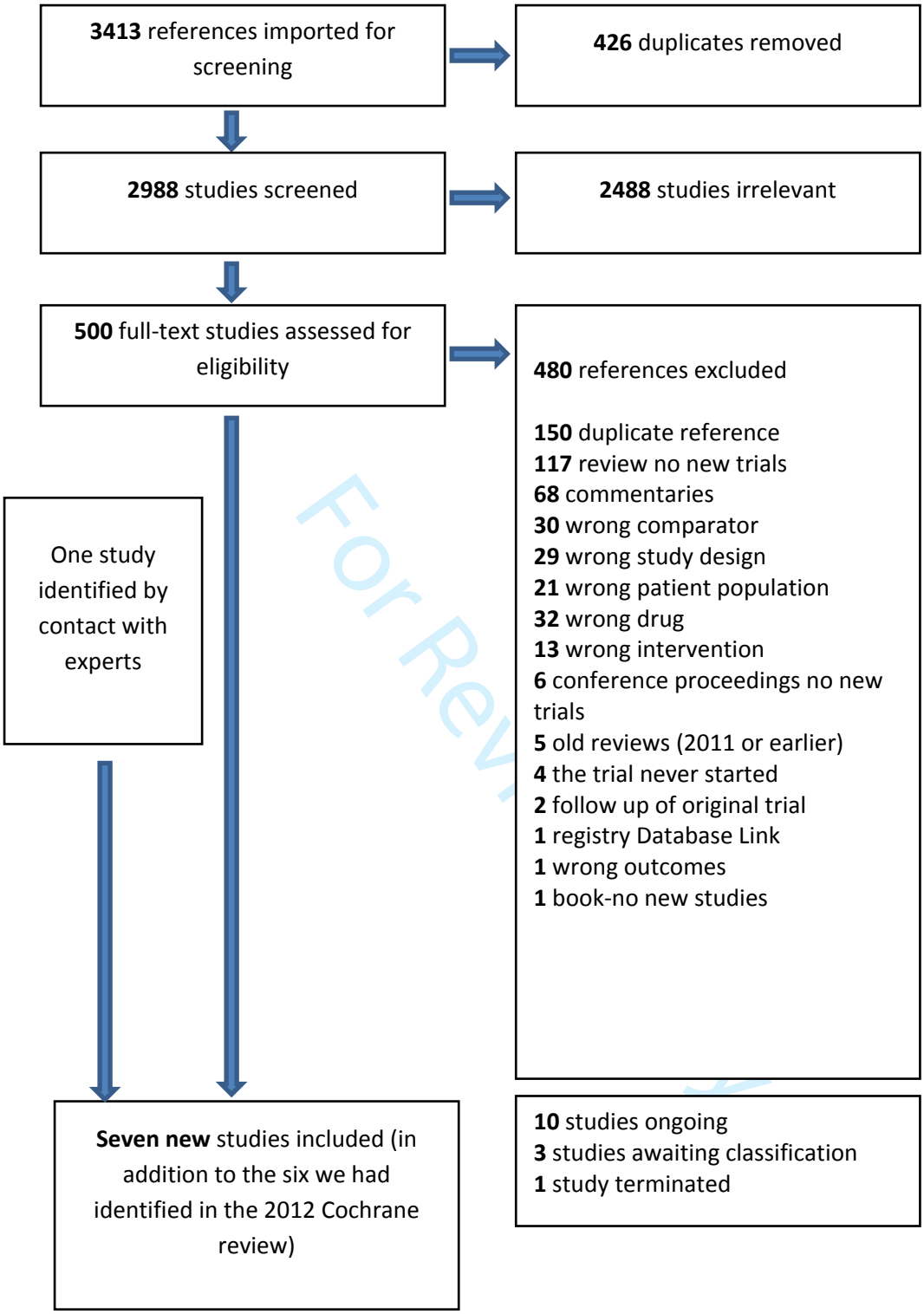
Legends for figures

Figure 1. Flow diagram showing selection of studies

Figure 2 Risk of Bias

Figure 3. Forest plot, mRS (0-2) at end of treatment

Figure 4. Forest plot, disability at end of treatment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117 review no new trials
68 commentaries
30 wrong comparator
29 wrong study design
21 wrong patient population
32 wrong drug
13 wrong intervention
6 conference proceedings no new trials
5 old reviews (2011 or earlier)
4 the trial never started
2 follow up of original trial
1 registry Database Link
1 wrong outcomes
1 book-no new studies
One study identified by contact with experts
Seven new studies included (in addition to the six we had identified in the 2012 Cochrane review)
10 studies ongoing
3 studies awaiting classification
1 study terminated